The Risks of Promoting Unapproved Uses

Why are manufacturers required to obtain approval for each new use of a prescription drug prior to distributing it for that use?

The premarket review and approval provisions of the Federal, Drug, and Cosmetic Act (FD&C Act) are designed to help prevent harm to patients from unsafe and ineffective medical products by having FDA review the safety and effectiveness of each new use of the medical product before it is distributed for that use. The FD&C Act also requires that a product's labeling bear adequate directions for each new use.

These provisions provide critical protection for public health by:

- Creating incentives to develop robust scientific data regarding the safety and efficacy of the medical product for a particular use. Otherwise, a firm could obtain approval or clearance for one use but then promote its product for an unapproved use, without conducting any scientifically robust clinical studies to assess the safety or efficacy of the unapproved use.
- Requiring the review of data before marketing of the product for that use in order to prevent harm and to better ensure that healthcare professionals have a sound basis for making treatment decisions, before the use is widespread.
- Providing the review of safety and efficacy data by an independent body to assure that the claims are appropriately supported.
- Requiring the development of labeling that provides information necessary for the safe and effective use of the product.

Why shouldn't pharmaceutical manufacturers be able to market their products for unapproved uses?

If firms promoted their products for unapproved uses, then the safeguards designed to protect the public health listed earlier would be compromised and could lead to patient harm, including:

- Direct harm from a product that is unsafe for unapproved use or that lacks adequate directions for such use;
- Use of ineffective therapies (e.g., an ineffective drug might be used in place of another drug that has been shown to be safe and effective, which may result in irreversible harm to the patient, such as worsening of a disease that would have responded to another therapy to a point that makes it more difficult or impossible to treat the disease); and
- Exposure of patients to the risks of an ineffective treatment.

History has shown that widespread acceptance of an unapproved use in the medical community is no guarantee that a drug or device is safe or effective for that use and is no substitute for rigorous clinical trial testing, development of FDA-required labeling, and careful scrutiny by FDA that the approval and clearance processes require. There have been many instances where acceptance of common treatment practices by the medical community have later been shown to be unsafe or ineffective, or both—sometimes with devastating consequences to public health. Examples follow.

- **Atypical Antipsychotics.** These drugs, which are generally approved for schizophrenia and bipolar disorder, were commonly used unapproved to treat behavior problems in elderly patients with dementia. Subsequent controlled trials have revealed increased mortality resulting from this use, primarily resulting from deaths due to cardiovascular events and infectious disease. These products now bear a boxed warning noting the risks of using them to treat elderly patients with dementia.
- **Premarin/Prempro.** Premarin (an estrogen) and Prempro (an estrogen plus a progestin), also known as menopausal hormone therapy, are approved for treating menopausal

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symptoms (including hot flashes) and preventing postmenopausal osteoporosis based on data from adequate and well controlled trials. Menopausal hormone therapy was extensively prescribed to women for long-term use in the hope that it would prevent the increase in the risk of coronary artery disease that follows menopause, a plausible hypothesis that was supported by some epidemiologic evidence but not by data from well-controlled clinical trials. When menopausal hormone therapy was finally rigorously studied in the Women's Health Initiative study (a large government-sponsored randomized placebo-controlled trial), it was found that estrogen and progesterone given to women increased their risk of vascular disease (including stroke, thromboembolic disease, and myocardial infarction). The risk was high enough to halt the planned eight-year study, three years before its scheduled cessation.

- **Encainide and Flecainide.** In the 1980s many physicians began to prescribe two anti-arrhythmic drugs, encainide and flecainide, to treat minor disturbances in heart rhythms (more than 10 ventricular premature beats per hour) that were known to be associated with decreased survival in patients who had recently experienced heart attacks. Many in the medical community hoped suppressing these irregular beats would improve survival in this population. The drugs were approved by FDA only for the treatment of life threatening ventricular arrythmias, and the product labeling specifically noted a lack of information on the performance of the drugs in the post-heart-attack setting. Subsequent clinical evaluation in a well-controlled study (the Cardiac Arrhythmia Suppression Trial, also called "CAST") by the National Institutes of Health for this use of the two drugs to treat heart rhythm disturbances in post-heart attack patients demonstrated that the patients who took those drugs and had a marked reduction in ventricular premature beats had about a 2.5-fold increase in the risk of mortality or cardiac arrest as compared to the patients given placebo.

July 2015